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*Original Research*

# Prognostic significance of pretreatment lymphopenia in colorectal cancer

Lymphopenia and colon cancer

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**Abstract**

Aim: It is proven that pretreatment lymphopenia is a biomarker for poor prognosis at late stage solid malignancies. The purpose of the present study is to investigate the effects of pretreatment lymphopenia on prognosis and hematological toxicity in patients treated with first step systemic chemotherapy. Material and Method: Lymphocytes were counted for 386 patients with colorectal cancer before treatment. Overall survival (OS), progression-free survival (PFS) and disease-free survival (DFS) were calculated. Results: Three hundred and eighty-six patients were included in the study. The mean age was 57.4. One hundred and sixty patients were women (41%), 226 were men (59%). Mean pretreatment lymphopenia was 1964/microliter. There was no relation between lymphopenia and age, gender, performance status, the presence of metastasis at the time of diagnosis, the purpose of chemotherapy either being adjuvant or metastatic and progression into hematological toxicity ($p > 0.05$). One-, two- and five-year overall survival was significantly lower in patients with lymphopenia when considering all patients ($p:0.033$). Lymphopenia was present in 27 patients (7%) who had metastasis at the time of diagnosis and 13 of them deceased in the follow-up. One-, two- and five-year overall survival was significantly lower in those patients with metastasis who have lymphopenia ($p < 0.043$). Discussion: The present study supports that pretreatment lymphocyte count in colorectal cancer can be a simple yet useful prognostic and predictive marker. Overall survival found to be significantly lower in patients with low pretreatment lymphocyte counts ($p < 0.05$). To the best of our knowledge, the present study has the largest patient population in the literature which investigates the relationship between colorectal cancer and lymphopenia.

**Keywords**

Colorectal Cancer; Lymphopenia; Prognosis

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## Introduction

Colorectal cancer is an important health issue as being the third most common cancer diagnosed and the second leading cause of cancer-related deaths. Several prognostic factors such as local invasion, regional lymph node involvement, the presence of micrometastasis, and vascular invasion are defined. Most of these factors are used during pathological staging [1]. The relation between the immune system and cancer is known for quite a long time. Lymphocytes are the most important component of the immune system. The decrease in lymphocyte count can lead to immune system deficiency. The relation between cancer and lymphopenia has been investigated in several different studies and it is shown that patients with lymphopenia have a poor prognosis [2]. The purpose of the present study is to investigate the prognosis of patients with colorectal cancer using an easy-to-use and cheap marker, lymphocyte count, at the time of the diagnosis.

## Material and Methods

Data of colorectal cancer patients who had been admitted to our center for 15 years were retrieved. Three hundred and eighty-six patients diagnosed with colorectal carcinoma and who did not have chemotherapy, radiotherapy or chemo-radiotherapy, granulocyte colony stimulating factor (G-CSF) for primary prophylaxis, HIV infections or bone marrow involvement, a secondary malignancy but had first chemotherapy and over 18 years of age were included in the present study. Age, gender, performance status, type of surgery, location of primary tumor, stage at diagnosis, purpose of chemotherapy, number of chemotherapy regimen, name of chemotherapy regimen, presence or absence of metastasis at diagnosis, location of metastasis at diagnosis, metastasis in the follow-up and if present, its location, relapse status are investigated retrospectively by scanning patient health records. Pretreatment leucocyte and lymphocyte counts were recorded, and it was assessed whether hematological toxicity developed or not, and if developed, the type of the toxicity, the degree of hematological toxicity and at which regimen and occurrence of additional toxicity were noted. Response type of treatment, disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS) are calculated. Duration of follow-up and whether they are alive were checked. Lymphopenia was defined as lymphocyte counts lower than 1300/microliter in our laboratory. The assessment of hematological toxicity was done according to the World Health Organization (WHO) toxicity criteria. The TNM Classification system is used for staging the disease. Preferred staging system in colorectal cancers is TNM Classification which formed by the American Joint Committee on Cancer (AJCC). This system enables staging cancer according to tumor dimensions and depth of invasion, the involvement of lymph node and metastasis. The system is being maintained and updated periodically [3]. The data were statistically analyzed using SPSS 17.0. Statistical analyses were performed by the Kaplan-Meier, the Chi-Square and the Student's t- tests and $p<0.05$ value was accepted as statistically significant.

## Results

One hundred and sixty of 368 patients were women (41.5%), 226 were men (58.5%). The mean age was 57.4 (21-81 years). Distribution of the tumor localizations is shown in Table 1.

There was no stage I patient among our cohort. There were 93 stage II (24.1%), 158 stage III (40.9%), and 135 stage IV patients. There was no metastasis at the time of diagnosis in 251 patients (65%). One hundred and twenty-six patients (32.6%) had one or two, 10 patients (2.6%) had three or more metastases. 106 patients (27.5%) had liver metastasis among 135 patients (35%) with metastasis at the time of diagnosis. At the time of diagnosis 87 patients (22.5%) had lymphopenia. Overall survival rates for the patients with or without lymphopenia are shown in Table 2.OS rates were statistically lower for the patients with lymphopenia at diagnosis (p:0.033).

Although DFS is shorter in the group with lymphopenia when 5-year disease-free survival according to lymphocyte counts at diagnosis compared, it was not significantly different (p:0.058). There was no significant difference in progression-free survival (PFS) when both groups with or without lymphopenia are compared (p:0.55). There was no significant difference in terms of age, gender, mean age, performance status, and metastasis at diagnosis, whether chemotherapy is adjuvant or palliative, the occurrence of hematological toxicity when both groups with or without lymphopenia are compared ($p>0.05$) (Table 3).

**Table 1.** The localizations of primary tumor

| Tumor site | Number of patients (n) | Percentage of patients (%) |
|---|---|---|
| Right colon | 97 | 25.1 |
| Transverse colon | 18 | 4.7 |
| Left colon | 52 | 13.5 |
| Sigmoid | 97 | 25.1 |
| Rectosigmoid | 21 | 5.4 |
| Rectum | 101 | 26.2 |
| Total | 386 | 100 |

**Table 2**. Mean survival rates among patients with or without lymphopenia

| | Patients with lymphopenia (n:87) | Patients without lymphopenia (n:299) |
|---|---|---|
| 1-year OS | 89% | 95% |
| 3-year OS | 67% | 80% |
| 5-year OS | 57% | 68% |

**Table 3**. Features of the patients with or without lymphopenia at the time of diagnosis

| Features | Lymphocyte<1300/microliter (n:87) | Lymphocyte >1300/microliter (n:299) | P- value |
|---|---|---|---|
| Gender (F/M) | 29/58 | 131/168 | p:0.08 |
| Mean age (year) | 57.3 | 57.4 | p:0.93 |
| ECOG (0-1/ >1) | 82/5 | 283/16 | P:0.79 |
| Metastasis at diagnosis (Absent/Present) | 57/30 | 188/11 | p:0.65 |
| Adjuvant / palliative Chemotherapy | 60/27 | 190/109 | p:0.35 |
| Hematological toxicityabsent/present | 60/27 | 220/79 | p:0.39 |

ECOG: Eastern Cooperative Oncology Group (ECOG) performance status is a scale used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

While 280 patients (72.5%) had no hematological toxicity, 106 patients (27.5%) developed toxicity. Types of hematological toxicity observed in our patients are shown in Table 4.

When assessed the severity of hematological toxicity among 106 patients (27.5%) who developed hematological toxicity, 66 patients (17.1%) had grade 1-2, 34 patients had (8.8%) grade 3, and 6 patients (1.6%) had grade 4 toxicities. A comparison between patients who developed grade 3-4 toxicity and others (no toxicity and grade 1-2 toxicity) are shown in Table 5. Grade 3-4 toxicity was significantly higher in patients received palliative chemotherapy when compared with the patients who received adjuvant chemotherapy.

In the group of 135 patients with metastasis, 13 patients among 27 patients who had lymphopenia, deceased at diagnosis. One hundred and five patients who had metastasis at diagnosis did not have lymphopenia and 31 of them deceased during the follow-up. There was a significant difference among the two groups (p:0.043). OS status according to lymphopenia for the patients with metastasis at diagnosis is shown in Table 6.

## Discussion

In order to estimate the prognosis, several clinical and pathological factors are defined; these can be features belonging to tumor (dimension of tumor, stage, molecular changes, local invasion, lymph node involvement, and vascular invasion), patient (age, performance status, inheritance of susceptibility, gender, ethnicity, and deficiency of vitamin D, obesity, and coronary artery disease), nature and quality of the therapy [4].

It is shown in several studies that lymphocytes play as positive regulators of immune response. In addition to ensuring host response against infection and inflammation, they are quite effective cells against cancer survival [5].

Lymphocyte count can be an indicator for host immune response. Prognosis of cancer depends on the aggressivity of tumor and immune response and the relation between lymphocyte count and cancer prognosis has been a long-standing research subject [6]. Several hypotheses has been suggested about the etiology of lymphopenia in cancer. Factors such as bone marrow involvement, cachexia, and hypoalbuminemia can contribute but the most acceptable two hypotheses suggest that lymphopenia is caused by the destruction of lymphocytes by tumor cells and/or deterioration of lymphocyte pool in cancer cells. Besides immune weakness, lymphopenia in cancer patients can also be related tochemotherapy toxicity, decreased response to chemotherapy, tumor progression, poor prognosis, and shortening of survival [7-9].

The relation between pretreatment lymphocyte counts and chemotherapy toxicity, survival and other parameters in solid and hematological malignancies (breast cancer, melanoma, cervical cancer, renal tumor, head-neck tumors, and lymphomas) are studied [10-13].

Although it changes due to the laboratory differences, the threshold value for lymphopenia is usually defined as <1000 / microliter. We accepted <1300/microliter as a threshold value. At the time of diagnosis, 22.5% of our patients had lymphopenia and this was compatible with the literature (19%,22%,28%) [14-16].

Mean age was similar in two groups (57.3 years/57.4 years) and there was no significant difference between lymphopenia and mean age. While there are similar results in the literature [17], there are studies which show that there is a significant relation between lymphopenia and age [18-20].

Development of hematological toxicity in cancer is a factor that shortens overall survival. Several different factors such as age, weight, gender, performance status, dietary status, organ functions, serum albumin and bilirubin levels, polymorphisms, drug application method have been defined in order to define hematological toxicity of chemotherapy in colorectal cancer patients [21].

In the present study, 27.5% of patients developed hematological toxicity and this rate is similar to the literature (% 10-49).

In the present study, lymphopenia did not increase hematological toxicity. However, a similar study investigating the relationship between colorectal cancer and lymphopenia showed that grade III-IV toxicity was related to lymphopenia at the time of diagnosis.

It would be significant to detect whether lymphopenia in cancer progression is a result or a cause. In some studies, correction of lymphopenia ensured full remission in solid malignancies with lymphopenia.

In the present study, the relationship between PFS and lymphopenia could not be shown. However, DFC and lymphopenia were related although it was not statistically significant; DFS was found to be better in patients without lymphopenia. In simi-

**Table 4.** Types of hematological toxicity observed in our patients

| Hematological toxicity | Number of patients (n) | Percentage |
|---|---|---|
| Absent | 280 | 72.5 |
| Neutropenia | 50 | 13 |
| Febrile neutropenia | 4 | 1 |
| Thrombocytopenia | 21 | 5.4 |
| Anemia | 31 | 8 |
| Total | 386 | 100 |

**Table 5.** A comparison between patients who developed grade 3-4 toxicity and others

| Parameters | No toxicity or grade 1-2 toxicity (n:346) | Grad 3 or 4 hematological toxicity (n:40) | p-value |
|---|---|---|---|
| Lymphopenia | | | |
| Yes | 80 | 7 | p:0.42 |
| No | 266 | 33 | |
| Mean age (year) | 57.0 | 60.8 | p:0.071 |
| ECOG | | | |
| 1-2 | 329 | 36 | p:0.256 |
| 3-4 | 17 | 4 | |
| Chemotherapy | | | |
| Adjuvant | 234 | 16 | p:0.001 |
| Palliative | 12 | 24 | |

**Table 6.** OS status according to lymphopenia for the patients with metastasis

| | Lymphocyte < 1300/microliter (n:27) | Lymphocyte > 1300/microliter (n:105) |
|---|---|---|
| 1-year OS | 74% | 89% |
| 2-year OS | 46% | 76% |
| 3-year OS | 28% | 48% |
| 5-year OS | 16% | 42% |

lar studies, DFS and PFS are in a significant relationship with lymphopenia. The most important result of the present study is that it proves the relationship between lymphopenia and overall survival similarly to previous studies [22,23].

Shorter one-, there-, five-year overall survival rates were detected in patients with lymphopenia likewise in other studies.

Shortening of survival in colorectal patients with lymphopenia is attributed to several different reasons. The first of these views is that host immunosuppression caused by lymphopenia decreases the response to therapy. Similarly, loss of antitumor-specific immune response due to lymphopenia can also trigger tumor progression. The other possible cause for shortening of survival is the occurrence of febrile neutropenia and related morbidity. In spite of the fact that only four among 106 patients had febrile neutropenia, it is observed that these patients could not receive their treatments on time and inadequate amounts due to dose restrictions. Prognosis of these patients was also poor as lymphopenia increased immunosuppression.

The advantage of the present study in which we obtained similar to literature lymphopenia and colorectal cancer survival rates is the excessive number of patients. The most important limitation of the present study is that the patients formed heterogeneous groups and received different regimens of chemotherapy.

In the light of the present study, it is recommended to form more homogenous groups and investigate patients who have similar chemotherapy regimens. It is going to play a critical role to show which particular lymphocyte subgroup decreased in colorectal cancer patients with lymphopenia, in order to confirm the results of the present study and bring in a correct follow-up parameter to the literature.

### *Conclusion*

Change of overall survival because of lymphopenia is highlighting the prognostic importance of lymphopenia. Change of hematological toxicity due to lymphopenia suggests a predictive role of lymphopenia. In the light of this information, we can suggest that lymphopenia has a prognostic importance in colorectal cancer patients. Although hematological toxicity was not found in patients with lymphopenia, this needs to be investigated in aforementioned homogenous patient cohort.

*Scientific Responsibility Statement*
***The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.***

*Animal and human rights statement*
***All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.***

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